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Refer to: Connors MH: Growth and maturation arrest, hypochromic anemia and hyperglobulinemia associated with a brain tumor. West J Med 133:160-163, Aug 1980

Growth and Maturation Arrest, Hypochromic Anemia and Hyperglobulinemia Associated With a Brain Tumor

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ARREST OF GROWTH and sexual maturation by brain tumors that increase intracranial pressure may be associated with hypothalamic-pituitary suppression.[1] This latter mechanism appeared relatively unimportant in the case of a teenage boy with short stature, sexual immaturity, refractory hypochromic anemia, hyperglobulinemia, hepatosplenomegaly and a brain tumor. Previously, the syndrome of a refractory form of hypochronic anemia, hypergammaglobulinemia and growth arrest had been reported associated with abdominal hamartomatous lymphoid tumors.[2] The finding of increased levels of growth hormone in the serum provides further information on this refractory clinical condition.

Report of a Case

The patient, a 15½-year-old boy, was referred to us because of arrest of growth, lack of sexual maturation and continued anemia despite iron therapy. From the age of 12½ years the boy's parents had noted a decrease in the rate of his growth; however, they did not seek treatment for this condition. The boy noted that during the first years of school he had been one of the biggest children in his class. Later, however, he was brought to his pediatrician because of the teasing he received over his small size. He was found to be anemic. Following a month of iron therapy (45 mg per day) with failure to respond, further evaluation of the boy's condition was requested. His father was 190.5 cm (6 foot 3 inches) and his mother 167.6 cm (5 foot 6 inches) tall. A 13-year-old brother was 10.2 cm (4 inches) taller than the patient.

The patient's only other complaint was frontal headaches every few months that would last a couple of days. There was no associated vomiting. He was otherwise active and doing well in school.

On physical examination the boy was found to be pleasant and freckle-faced. Head circumference was 56 cm (mean for that age), height 147.5 cm (4 feet 8 inches) and weight 37 kg (81.6 pounds) —both less than the 5th percentile and mean for 11½ years. The skeletal age was 10 years. Blood pressure was within normal limits. Funduscopic examination showed bilateral papilledema and tortuous veins. A defect in the right superior quadrant was found on visual field testing. The liver was palpated 4.5 cm below the right costal margin and the spleen was enlarged 2.5 cm below the left costal margin. Both were smooth and not tender. The testes were descended and measured 1.6 cm in their longest diameter. The penis was 7.5 cm in length. No pubic or axillary hair was present. No abnormalities were found on neurological testing.

Studies of the blood (Table 1) gave the following values: hemoglobin 8.0 grams per dl, with 1.0 percent reticulocytes and a corrected sedimentation rate of 140 mm per hour. Erythrocyte

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Submitted, revised, October 31, 1979.

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TABLE 1.—*Laboratory Data Before and After Treatment of Brain Tumor*

Time	Hemoglobin (grams/dl)	Hematocrit (percent)	Iron-Binding Capacity (μg/dl)	Serum Protein			Immunoglobulins		
				Total (grams/dl)	Albumin (grams/dl)	Globulin (grams/dl)	Gamma G (mg/dl)	Gamma A (mg/dl)	Gamma M (mg/dl)
Preoperation	8.0	26.2	266	9.2	2.9	6.3	2,690	1,050	200
Postoperation									
16 days	11.3	34.3	236	7.5	3.2	4.3	..	..	..
6 months	10.3	31.1	254	7.8	3.5	4.3	1,660	1,220	170
12 months	9.3	29.2	..	6.8	3.4	3.4	..	..	..

count showed a mean corpuscular volume of 55 μ^3, mean corpuscular hemoglobin of 17.1 $\mu\mu$g and mean corpuscular hemoglobin concentration of 30.7 percent. The bone marrow had 50 percent cellularity with a myeloid-erythroid ratio of 1:1. Maturation of all cell lines was normal. Plasma cells made up 5 percent to 10 percent of the nucleated cells. On staining, no iron was seen. The level of iron in the serum was low (38μg per dl) as was the total iron-binding capacity (266 μg per dl).

Blood chemistry measurements for electrolytes, glucose, urea nitrogen, creatinine, uric acid, bilirubin, calcium, inorganic phosphate and cholesterol were within normal range. However, the level of alkaline phosphatase in the serum was elevated: 384 mU per ml heat stabile and 216 mU per ml heat labile (normal for age, 400 mU per ml total, with heat stabile less than 25 percent). Liver enzyme levels were normal. Partial thromboplastin time was 41.6 seconds with a control time of 33 seconds. Prothrombin time was 14.4 seconds with an 11-second control time. The quantitative fibrinogen concentration was elevated at 1,100 mg per dl and no fibrin split products were noted.

Analysis of urine showed an osmolality of 703 mOsm with proteinuria (2+). Electrophoresis of this protein showed 16.8 mg per dl of albumin; the globulins measured: alpha-1 11.8, alpha-2 30.4, beta 22.4 and gamma 18.6 mg per dl.

Radiographic studies included normal skull and sella turcica findings. On admission a computerized axial tomographic (CAT) scan was carried out. The findings were interpreted as normal. However, a repeat scan with contrast material showed a large enhancing homogeneous mass along the left margin of the tentorium. Cerebral angiography defined the mass above and below the tentorium on the left side.

Endocrine evaluation indicated normal thyroid function with serum thyroxin at 9.6 μg per dl and thyroid-stimulating hormone levels within normal limits. Insulin tolerance testing was carried out using regular insulin (0.1 unit per kg of body weight, given intravenously as a bolus). The fasting serum glucose concentration decreased from 88 to 53 mg per dl at 30 minutes and returned to 76 mg per dl at 60 minutes. Concentration of human growth hormone was elevated to between 12 and 15 ng per ml resting and rose to 23 ng per ml at 30 minutes. There was no increase in the concentration of serum cortisol (11 μg per dl) following the decrease in concentration of serum glucose. Analysis of a 24-hour specimen of urinary steroid metabolites showed normal levels of 17-ketosteroids (6 mg) and 17-ketogenic steroids (10 mg) for his size.

In preparation for the surgical operation, the patient was given fresh frozen plasma to correct defects in coagulation. Cold agglutinins and difficulty in cross matching for blood transfusion were noted. During the operation the tumor was detected immediately upon elevation of the occipital lobe. The tumor bled freely and several hours were required to carefully remove tumor tissue from above and below the tentorium. Because of its attachment near the straight sinus, the tumor was trimmed as much as was felt safe; approximately 85 percent of the tumor mass was removed. The type of the tumor could not be identified from frozen sections. Following permanent fixation of the tumor tissue the histologic diagnosis has remained controversial. One neuropathologist found the tissue specimen suggestive of a chordoma while consultants from the Armed Forces Institute of Pathology suggested that the tissue represented an unusual variant of an angioblastic meningioma of the hemoangioblastic type. During the patient's recovery, there was a decrease in the size of the liver and spleen and hematologic studies showed improvement.

Six months following the surgical operation, the patient had five weeks of radiotherapy, with a total dose of 5,000 rads administered to the posterior fossa. At that time, the boy's height had increased 3.8 cm (1.5 inches) (Figure 1). No disturbances of vision were noted. Evidence of

sexual maturation included larger testes (3 cm bilaterally) and pubic hair.

Measurement of serum growth hormone was 2.0 ng per ml at rest, and serum gonadotropin and testosterone levels were appropriate for the stage of puberty. A CAT scan showed no change in the residual tumor. Hematologic findings were slightly worse (Table 1); however, there was no enlargement of the liver or spleen.

A year following the operation, the patient's growth and pubertal maturation had progressed further (Figure 1). At that time, the level of resting serum growth hormone, 1.2 ng per ml, was within normal limits.

Discussion

The association of hypochromic anemia, hypergammaglobulinemia and arrest of growth has been reported by Neerhout and co-workers[2] in association with a mesenteric lymphoid hamartoma. In their review of the literature, they found two other cases with similar characteristics, with the exception of growth failure in one, and associated with mediastinal or abdominal lymphoid masses. There was reversal of symptoms with removal of the tumor. Although the identification of the tumor type in our patient has been controversial, it in no way resembles the lymphoid hamartomas described in these cases. Also, the tumor under discussion here had no relationship to the pineal body. Cell mitoses were rarely seen and the tumor was apparently not frankly malignant.

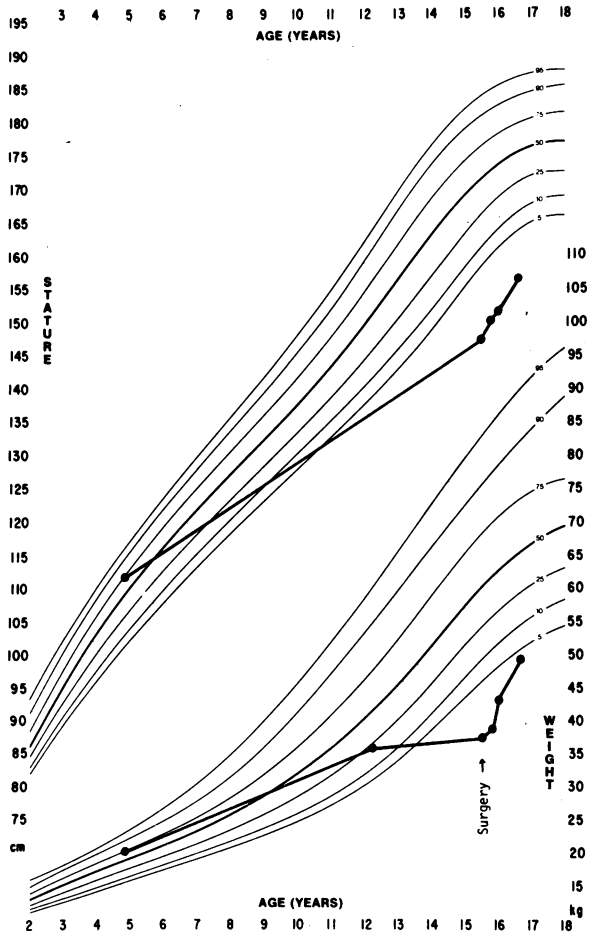

Figure 1.—Above average size is shown for the patient at 4 years 9 months of age, as well as accelerated pattern of growth following removal of tumor.

Despite the difference in location and pathological aspects of the tumor, the clinical features were quite similar to those previously reported. The low levels of serum iron, low iron-binding capacity and refractoriness to iron therapy present in all of the cases remains unexplained. Whether the persistent proteinuria results in transferrin deficiency cannot be answered. In our patient these features did not improve with partial removal and irradiation of the remaining tumor tissue. Splenomegaly and hepatomegaly resolved after the operation despite continued elevated levels of gamma globulins.

Intact pituitary function was supported by the findings of normal thyroid and adrenal function. The failure of the cortisol level to rise in the presence of hypoglycemia may result from the inadequacy of the stress. The prompt return to a normal serum glucose concentration following this test is supportive of intact pituitary-adrenal function as are the normal concentrations of adrenal metabolites in the 24-hour urinary specimen. Cortisol insufficiency by itself may be associated with increased linear growth.[3] The finding of increased levels of growth hormone at rest may indicate a refractory state to growth hormone. Occasionally in a child, there may be elevated levels of growth hormone at rest because of anxiety. The two baseline determinations of growth hormone, done 30 minutes apart, were both elevated in our patient, and the resting cortisol level did not reflect any unusual stress. Similar resting growth hormone elevations have been reported in cases of severe protein calorie malnutrition such as kwashiorkor.[4] In this condition, increased levels of growth hormone are associated with a low to absent concentration of somatomedin. With protein repletion there is a reversal of symptoms. The genetic form of growth

hormone resistance is found in the case of Laron dwarfism, where growth hormone levels are elevated while somatomedin concentrations are low.[5] It has been suggested that growth hormone may influence erythropoietin[6]; however, this effect is not a pronounced one, nor is it clinically apparent in children with isolated growth hormone deficiency or Laron dwarfism. Unfortunately, measurements of somatomedin were not done in this study to support this possibility.

The catch-up growth that occurred in our patient was associated with a return to normal levels of measurable growth hormone and the onset of puberty. It is, therefore, difficult to separate these influences on the acceleration of the boy's growth, and it is likely that both were needed.[7] The possibility that release of gonadotropin occurred as the result of the brain operation, thereby stimulating puberty is also a consideration. Other authors[8] have reported pituitary insufficiency following radiation therapy to the brain that excludes the pituitary gland.

The accelerated growth seen in patients after removal of lymphoid hamartomas favors a systemic influence. However, no hormonal measurements are available in these studies. Because of the clinical similarity in our patient's course following the operation, a similar mechanism is favored.

Summary

A brain tumor developed in a 15½-year-old boy with associated arrest of growth (despite the presence of growth hormone) and of sexual maturation, refractory hypochromic anemia and hyperglobulinemia. A similar clinical triad has been reported with lymphoid hamartomas, although the tumor did not resemble this type of tissue growth. After partial removal of the tumor, catch-up growth and sexual maturation occurred with minimal improvement in the anemia. These observations indicate that certain tumors through associated immunological mechanisms have an etiologic role in this clinical pattern.

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Refer to: Nierenberg DW: Furosemide and ethacrynic acid in acute tubular necrosis. West J Med 133:163-170, Aug 1980

Furosemide and Ethacrynic Acid in Acute Tubular Necrosis

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OLIGURIC ACUTE RENAL FAILURE (ARF) is a syndrome characterized by a rapid decrease in renal function with progressive azotemia and oliguria (urine output of 50 to 400 ml per 24 hours).[1] Major causes of this syndrome are prerenal azotemia (such as volume depletion), postrenal obstruction (such as prostatic hypertrophy), renovascular disease (such as renal artery emboli) and parenchymal renal disease (such as glomerulitis or acute tubular necrosis).[1,2] By far the most common cause of ARF is acute tubular necrosis (ATN), which represents about 75 percent of all cases.[1]

Mannitol has been recommended for both diagnosing and treating ARF, although considerably more is known about the use of the loop diuretics furosemide and ethacrynic acid in this syndrome. It has been proposed that a successful diuresis in response to large intravenous boluses of these latter drugs helps differentiate prerenal azotemia from ATN.[3] Others have suggested that furosemide and ethacrynic acid are effective in

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